IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of Saidi, Zahir et al.	:	Confirmation No. 8648
Application Serial No.: 10/019,100	:	Group Art Unit: 1627
Filed: August 21, 2003	:	
For: AQUEOUS COMPOSITIONS CONTAINING CORTICOSTEROIDS FOR NASAL AND PULMONARY DELIVERY	:	Examiner: Layla Soroush

FILED ELECTRONICALLY ON USPTO EFS-WEB ON MARCH 2, 2010 BY MARISSA T. GERARDO FOR VYACHESLAV V. VASILYEV, REG. NO. 58,154

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APPEAL BRIEF

SIR:

This Brief is in response to the Office Action of April 15, 2009, relating to the above-identified patent application.

The fees required under 37 C.F.R. § 1.17(h) are paid along with the accompanying TRANSMITTAL OF APPEAL BRIEF. Commissioner is hereby

authorized to charge any fees in connection with this appeal, or with any other related matters before the PTO, to the undersigned's Deposit Account No. 50-1943.

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II. TABLE OF AUTHORITIES

Statutes

35 U.S.C. § 103

Rules and Regulations

MPEP § 2111.03

MPEP § 2145.X.D.

MPEP § 804[R-5].II.B.1.

Cases

In re Fulton, 391 F.3d 1195, 1201 (Fed. Cir. 2004)

General Foods Corp. v. Studiengesellschaft Kohle mbH, 972 F.2d 1272, 1279 (Fed. Cir. 1992)

Titanium Metals Corp. of America v. Banner, 778 F.2d 775 (Fed. Cir. 1985)

In re Gordon, 733 F.2d 900 (Fed. Cir. 1984)

In re Edge, 359 F.2d 896, 149 USPQ 556 (CCPA 1966)

In re Wesslau, 353 F.2d 238, 241 (CCPA 1965)

In re Aller, 220 F.2d 454, 456 (CCPA 1955)

In re Gray, 53 F.2d 520, 11 USPQ 255 (CCPA 1931)

Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)

III. REAL PARTY IN INTEREST

The real party in interest hereto is the Assignee, Elan Pharma International, Ltd, a corporation having a place of business at Monksland, Athlone Co. Westmeath, Ireland.

IV. RELATED APPEALS AND INTERFERENCES

Applicants or the Assignee are not aware of any related appeals and/or interferences.

V. STATUS OF CLAIMS

Claims 1, 6, 10, 13-17 and 22-27 are under consideration. Each of these claims has been previously presented to the Examiner. Each of these claims has been twice or finally rejected and is appealed now. Claims 2-4, 11 and 12 have been cancelled, claims 5, 7-9, 18-21 and 28-33 have been withdrawn.

VI. STATUS OF AMENDMENTS

No amendments have been filed after the Final Rejection of April 15, 2009.

VII. SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 of the instant invention is drawn to compositions consisting of: (a) from about 5 μg/ml to about 5 mg/ml of a corticosteroid in dissolved form; (b) from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component, wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E, wherein said ethoxylated derivative of vitamin E is the sole vitamin E component of the composition; and (c) at least about 70 weight percent aqueous phase.

The support for this claim is found at least in the originally filed claim 12 (p. 26, lns 11-18). Additional support is provided on page 8, lns 11-15 disclosing the composition wherein the corticosteroid is dissolved in vitamin E TPGS and the resulting concentrated solution is further dissolved in aqueous phase. Further support is provided on p. 8 ln 26- p. 9 ln 9 disclosing various corticosteroids including budesonide.

Independent claim 15 of the instant invention is drawn to a composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, consisting of:

(a) from about 5 μg/ml to about 5 mg/ml of a corticosteroid in dissolved form;

(b) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E, wherein said ethoxylated derivative of vitamin E is the sole vitamin E component of the composition;

(c) at least about 70 weight percent aqueous phase; and

(d) from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable cosolvent comprising propylene glycol, polyethylene glycol having a molecular weight between about 200 and 4000, glycerol, ethoxydiglycol, glycofurol, and ethanol, or a combination thereof.

The support for the claim is provided in the at least in the originally filed claim 12 (p. 26, lns 11-18) and claim 16 (p. 27, lns 1-4). Additional support is

provided on page 8, lns 11-15 disclosing the composition wherein the corticosteroid is dissolved in TPGS and the resulting concentrated solution is further dissolved in aqueous phase. Further support is provided on p. 8 ln 26- p. 9 ln 9 disclosing various corticosteroids including budesonide.

Independent claim 16 of the instant invention is drawn to a composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, consisting of:

(a) from about 5 μg/ml to about 5 mg/ml of a corticosteroid in dissolved form;

(b) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E, wherein said ethoxylated derivative of vitamin E is the sole vitamin E component of the composition;

(c) at least about 70 weight percent aqueous phase; and

(d) from about 0.1 to about 3 percent by weight of a low HLB surfactant having an HLB below about 8.

The support for the claim is provided in the at least in the originally filed claim 12 (p. 26, lns 11-18) and claim 16 (p. 27, lns 6-7). Additional support is provided on page 8, lns 11-15 disclosing the composition wherein the corticosteroid is dissolved in TPGS and the resulting concentrated solution is further dissolved in aqueous phase. Further support is provided on p. 8 ln 26- p. 9 ln 9 disclosing various corticosteroids including budesonide.

Independent claim 17 of the instant invention is drawn to a composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, consisting of:

(a) from about 5 μg/ml to about 5 mg/ml of a corticosteroid in dissolved form;

(b) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E, wherein said ethoxylated derivative of vitamin E is the sole vitamin E component of the composition;

(c) at least about 70 weight percent aqueous phase; and

(d) from about 0.1 to about 3 percent by weight of an oil.

The support for the claim is provided in the at least in the originally filed claims 12 (p. 26, lns 11-18) and 17 (p. 27, lns 9-10). Additional support is provided on page 8, lns 11-15 disclosing the embodiments wherein the corticosteroid is dissolved in TPGS and the resulting concentrated solution is further dissolved in aqueous phase. Further support is provided on p. 8 ln 26- p. 9 ln 9 disclosing various corticosteroids including budesonide.

VIII. GROUNDS OF REJECTIONS TO BE REVIEWED.

A. Whether the Examiner erred in concluding that claims 1, 6, 10, 13-17, and 22-27 are obvious under 35 U.S.C. § 103 in view of US Patent 6,193,985 to Sonne.

B. Whether the Examiner erred in concluding that claims 1, 6, 10, 13-17 and 22-27 are unpatentable in view of claims 1-7 of a U.S. Patent No. 6,241,969 under the doctrine of obviousness-type double patenting and in view of the Terminal Disclaimer filed on November 29, 2007.

IX. ARGUMENT

For the convenience of the Board, Applicants respectfully provide the prosecution history of the instant application to consider the rejections in the proper context. After the summary of the prosecution history, Applicants provide the reasons for withdrawing the rejections based on Sonne and U.S. Patent No. 6,241,969.

A. Prosecution history of the application.

This application is a national stage of PCT/US99/14351 (the '351 PCT application), which derives priority from U.S. application 09/105,838, now US Patent 6,241,969. At the time of national stage entry, the instant application contained 33 claims, out of which claims 2-4 and 11 were cancelled. Thus, claims 1, 5-10, and 12-33 were present in the application. Exhibit A.

On March 12, 2007, in response to Restriction/Election Requirement of October 10, 2006 (Exhibit B), Appellants elected to prosecute claims 1, 5-10, 12-17 and 22-27 (Exhibit C). Thus, claims 18-21 and 28-33 had been withdrawn. The Restriction/Election Requirement also included a request to elect a species of a corticosteroid active ingredient. Applicants elected budesonide. Accordingly, the Examiner withdrew claims 5, and 7-9 as directed to non-elected species.

On November 29, 2007, in response to an Office Action of May 31, 2007 (Exhibit D), Appellants cancelled claim 12 and amended claims 1 and 13-17. Exhibit E.

On August 11, 2008, in response to an Office Action of February 11, 2008 (Exhibit F), Appellants amended claims 1 and 15-17 into their current form. No amendments to the dependent claims have been made.

As of the day of this appeal, claims 2-4, 11 and 12 are cancelled, claims 5, 7-9, 18-21 and 28-33 have been withdrawn.

The Board of Patent Appeals and Interferences has the jurisdiction over this appeal pursuant to 35 U.S.C. § 134(a).

This appeal is taken from the Final Rejection of April 15, 2009. The Rejection set a three-month shortened statutory period for response. Claims 1, 6, 10, 13-17, and 22-27 have been twice or finally rejected. A Notice of Appeal is filed on July 15, 2009. The time for filing the Appeal Brief is within two months from the filing of the Notice of Appeal. Bd. R. 41.37(c). This Appeal brief is being filed on September 15, 2009.

The first rejection the Appellants ask the Board to reverse is that the rejection of claims 1, 6, 10, 13-17, and 22-27 as obvious in view of US Patent 6,193,985 to Sonne (Exhibit G).

B. Rejection of claims 1, 6, 10, 13-17 and 22-27 as obvious over Sonne should be withdrawn.

The 15 April 2009 Final Office Action rejects the above-captioned claims as obvious in view of Sonne. More specifically, page 4 of the rejection acknowledges that Sonne fails to exemplify a composition:

> wherein said ethyoxylated derivative of vitamin E is the sole vitamin E component in the composition, (**Appellants' independent claims 1, 15, 16, 17**)
>
> comprising a high HLB surfactant component of at least 50%, 75%, 90% by weight tocopheryl polyethylene glycol 1000 succinate (**Appellants' claims 10, 13, 14, 22, 23, 28, 30, and 32**),
>
> containing from about 0.1 to about 0.2 percent by weight of a pharmaceutically acceptable cosolvent comprising propylene glycol, polyethylene glycol having a molecular weight between 200 and 4000, glycerol, ethoxydiglycol, glycofurol, and ethanol, or a combination thereof (**Appellants' claim 15**),

containing 0.1 to about 0.3 percent by weight of phospholipids (**No pending claim recites this limitation**), or

containing 0.1 to about 3 percent by weight of an oil (**Appellants' claim 17**).

Despite the above failings of Sonne, the Examiner drew the conclusion that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to optimize the composition by substituting the alpha-tocopherol of Example 15 with a Vitamin E-TPGS and incorporating additional ingredients ...." (Final Office Action page 4).

Appellants focused their responses on the fact that the pending independent claims (Claims 1, 15, 16, and 17) recite the transition phrase "consisting of" and require that "said ethyoxylated derivative of vitamin E is the sole vitamin E component in the composition." In order to meet the limitations of the instant claim and exclude other non-listed elements, one skilled in the art would have to remove the alpha-tocopherol element of the composition in Sonne and only use the ethyoxylated derivative of vitamin E (vitamin E-TPGS).

The Examiner's response in the Final Office Action acknowledged that "the reference [Sonne] does not exemplify the sole use of vitamin E-TPGS in a composition, [but] one of ordinary skill in the art would have been readily motivated to utilize a tocopherol derivative in order to produce an efficient, non-irritating, and stable emulsion because Sonne teaches the use of a tocopherol or a derivative thereof." (Final Office Action Pages 4 and 5).

In support of maintaining the rejection, the Examiner relies on the disclosure of Sonne that states the use of a tocopherol or derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologic active agents. The Examiner uses this disclosure to support an assertion that one of ordinary skill in the art would, after reading Sonne, understand that one could use vitamin E-TPGS alone without a tocopherol or derivative thereof in the composition. (Final Office Action page 4).

By this Appeal, Appellants request the Board reverse the Examiner's rejection that claims 1, 6, 10, 13-17, and 22-27 are obvious in view of US Patent 6,193,985 to Sonne. With respect to this ground of rejection, Appellants make clear for the Board that separate grounds for patentability exist for each of the following groups of claims: (a) claims 1, 6, 10, 16, and 22-25 stand and fall together, (b) claims 13, 14, 15, 26, and 27 stand and fall together, and (c) claim 17

stands and falls independently of the other claims (noting that claims 1, 15, 16, and 17 are independent claims). Appellants present their arguments according to the grouping of claims.

1. Claims 1, 6, 10, 16, and 22-25.

The Examiner's position articulated above is inconsistent with the teachings of Sonne for at least the following reasons:

a. Removal of Sonne's tocopherol-based solvent and retention of its desired function is evidence of non-obviousness;

b. Sonne defines Vitamin E-TPGS as an emulsifier, not as a tocopherol derivative solvent clearly distinguishing those functionalities;

c. There is no reasonable expectation of success from Sonne that use of the vitamin E-TPGS emulsifier as a sole vitamin E compound is sufficient to administer insoluble drugs in a stable emulsion;

d. Removal of Sonne's tocopherol-based solvent is not routine experimentation because Sonne did not disclose the basic conditions of the instant claims.

These reasons are discussed in turn.

a. Removal of an element and retention of its function is indicia of non-obviousness.

Independent claims 1 and 16 recite the transition phrase "consisting of" and include the limitation that "said ethyoxylated derivative of vitamin E is the sole vitamin E component in the composition."

The transition phrase "consisting of" in the Appellants' independent claims excludes any element, step, or ingredient not specified in the claims. *In re Gray*, 53 F.2d 520, 11 USPQ 255 (CCPA 1931); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) MPEP 2111.03. Accordingly, in order for Appellants' claims to read on the prior art, the art must use only that which is expressly recited in Appellants' claim.

In the present case, Sonne requires a component that is excluded from Appellants' claim by use of the "consisting of" transition phrase, and by express claim language. Appellants' independent claims recite "vitamin E is the sole vitamin E component in the composition." In contrast, Sonne requires α-tocopherol solvents and the vitamin E-TPGS emulsifier. Sonne never uses E-TPGS alone. This fact is acknowledged by the Examiner.

Appellants respectfully submit that the instant composition removes an important element present in Sonne and yet retains its function. Appellants further

respectfully note that it has been well-settled law that the omission of an element and retention of its function is an indicia of unobviousness. See *In re Edge*, 359 F.2d 896, 149 USPQ 556 (CCPA 1966) (the claims drawn to business bonus cards having two layers directly bonded to each other were held not obvious over the references disclosing a similar card having two layers bonded to each other through an intermediate layer because the claimed cards contained functionality of the intermediate layer of the prior art).

In this case, it is unarguable that the instant claims exclude elements suitable as solvents according to Sonne, namely α-tocopherol, acetate, linoleate, nicotinate and hemi-succinate derivatives thereof. Yet the function of these compounds (which is to dissolve the active agent) is retained: the active agent is still dissolved and useful emulsions are formed.

Accordingly, for this reason the compositions of claims 1, 6, 10, 16 and 22-25 are not obvious in view of Sonne.

b. Sonne defines vitamin E-TPGS as a tocopherol derivative emulsifier, not as a tocopherol derivative solvent – clearly distinguishing those functionalities.

It is well settled law that the prior art references should be considered as a whole. "It is impermissible within the framework of section 103 to pick and

choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art". *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965). Contrary to that legal principle, the Examiner analyzes Sonne by picking and choosing only the portions of the disclosure which support her position.

The Examiner would have the Board conclude that one of ordinary skill in the art reading Sonne would either substitute the vitamin E-TPGS emulsifier for the tocopherol solvent or use the vitamin E-TPGS emulsifier alone without the presence of the tocopherol solvent. Such a conclusion is not supported by the proper consideration of Sonne as a whole.

i) The disclosure of Sonne leads to a conclusion that solvents and emulsifiers are not equivalent to each other.

Sonne discloses that "that certain tocopherol derivatives are efficient, non-irritant emulsifiers for such drugs, when dissolved in a tocopherol-based solvent." Sonne col 2, lns 59-62, emphasis added. Thus, these "certain tocopherol emulsifiers" and "tocopherol-based solvents" are clearly distinguished from each other, with the implication that solvents and emulsifiers are not equivalent to each other.

Sonne further discloses the lists of suitable solvents and suitable emulsifiers. The solvents include tocopherol and nicotinate, linoleate, acetate and hemisuccinate esters thereof, and various co-solvents, such as "[v]egetable oils such as sesame- or olive- or fractionated coconut oil, alcohols such as ethanol, propylene glycol, glycerol, polyethylene glycol or benzyl alcohol; or triacetin, see Sonne, Col. 6, lns 51-54. Emulsifiers include Vitamin E TPGS and various non-tocopherol emulsifiers (e.g., phospholipids, polysorbates, sorbitan esters of fatty acids, cetearyl glucoside or poloxamers, See Sonne, Col. 4, lns 50-53).

Thus, the lists of suitable solvents and emulsifiers do not overlap. Therefore, according to Sonne, suitable emulsifiers are not proper solvents and suitable solvents are not proper emulsifiers. In other words, Sonne provides support for a proposition that emulsifiers and solvents are not art-recognized equivalents, and therefore, are not interchangeable.

ii) Sonne does not suggest that vitamin E TPGS may be used as a solvent.

In addition to the lack of a general teaching of interchangeability of solvents and emulsifiers, Sonne does not suggest that a specific compound, Vitamin E

TPGS, is a suitable solvent. Sonne, at Col. 3, lines 5-31, defines the term "tocopherol" to include derivatives, such as ester derivatives. Appellants are not arguing that vitamin E-TPGS is not a tocopherol derivative. Rather, Appellants argue that Sonne differentiates vitamin E-TPGS as a unique tocopherol derivative which was described in Sonne as suitable for being used as an emulsifier rather than a solvent. Appellants also submit that while Sonne does note that certain derivatives of α-tocopherol may act as emulsifiers, it is not fair to simply assume that the derivatives which are useful as emulsifiers are also suitable solvents, especially considering Sonne in its entirety.

According to Sonne, certain tocopherols or their derivatives act as solvents by allowing substantially insoluble or sparingly soluble active agents to be dissolved therein. Col. 3, lines 1-4. Sonne surprisingly found, however, that a specific tocopherol derivative, not disclosed as a solvent, namely vitamin E-TPGS, acts as a non-irritating emulsifier which, according to Sonne, is advantageous over commercial emulsifiers such as phospholipids. Col. 4, lines 24-37. As such, Sonne distinguishes the vitamin E-TPGS emulsifier from the typical tocopherol derivative solvents. Thus the invention in Sonne is directed to the use of a tocopherol or derivative solvent other than Vitamin E TPGS, *in combination with* a tocopherol derivative emulsifier, namely vitamin E-TPGS.

While the Examiner quotes from Sonne extensively, the fact remains that Vitamin E TPGS is never mentioned in Sonne as a solvent. Critical analysis of Sonne supports the position that while Vitamin E TPGS is a suitable emulsifier, it is not suggested as a suitable solvent. In fact, Sonne implicitly excludes Vitamin E TPGS from the list of suitable solvents. For example, Appellants refer to Col 5, ln 65 – Col. 6 ln 2:

> The active ingredient can be dissolved in the lipid fraction of the tocopherol solvent and other solvents may be added if desired. The emulsifier, e.g. Vitamin E TPGS, and optionally other emulsifiers, can be added to either the oil and/or the water phase.

Thus, according to Sonne, the active ingredient is dissolved in the tocopherol solvent, the emulsifier, such as Vitamin E TPGS, is added to an oil and/or water phase, and then the phases are mixed. If the term "tocopherol solvent" of the quotation above encompassed Vitamin E TPGS, as the Examiner asserts, then the quotation would make no sense from the scientific and logical perspectives: i.e., the active ingredient can be dissolved in Vitamin E TPGS solvent and then the emulsifier such as Vitamin E TPGS is added to oil and/or water phase. In other words, if Vitamin E TPGS is a solvent, as the Examiner asserts, and Vitamin E

TPGS is also an emulsifier, then why distinguish the functionalities of the first and the second portions of TPGS? Why add Vitamin E TPGS emulsifier if it is already present in the composition as a solvent? In addition, such an interpretation would render the second sentence essentially meaningless.

Appellants also respectfully note that Sonne at Col 4, lns 40-44 mentions that "[s]table emulsions may readily be achieved according to the invention using a range of tocopherols or derivative compounds as solvents, with Vitamin E TPGS as emulsifier." *Emphasis added*. The fact that Sonne explicitly recited Vitamin E TPGS as an emulsifier strongly suggests that it is excluded from the list of suitable solvents.

The claims of Sonne also specifically exclude Vitamin E TPGS from the list of solvents and recite tocopherol derivatives useful as solvents as limited to "tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof." See Sonne, Col 15, lns 42-46.

Appellants further submit that exclusion of Vitamin E TPGS from the list of solvents is not a simple unintentional omission. It logically follows that since the recitation of specific tocopherol-based solvents does not include Vitamin E TPGS, and since Vitamin E TPGS is explicitly mentioned as an emulsifier, Vitamin E TPGS is neither disclosed nor suggested as a solvent.

Even the quotations of Sonne provided by the Examiner support the position that Vitamin E TPGS is disclosed as an emulsifier and not as a solvent. For example, the Examiner on page 4 of the Office Action cites to the passage in Sonne that "tocopherol derivatives, particularly certain esters, may themselves form efficient, non-irritating emulsifiers to enable stable emulsions to be formed." *Emphasis added*. On page 5 of the Office Action, the Examiner concludes that "the tocopherol derivative emulsifier of the invention may be used alone or in conjunction with other known emulsifiers…" *Emphasis added*.

Therefore, in view of the above, Appellants respectfully submit that removal of Sonne's tocopherol-based solvent and/or its substitution with Vitamin E TPGS is neither disclosed nor suggested by Sonne.

c. There is no reasonable expectation of success from Sonne that use of the vitamin E-TPGS emulsifier as a sole vitamin E compound is sufficient to administer insoluble drugs in a stable emulsion.

The Examiner has not provided any evidence that a person of the ordinary skill in the art would have a reasonable expectation of producing an emulsion of a poorly water soluble drug without a hydrophobic tocopherol-based solvent, as disclosed in Sonne. While the Examiner concludes that there is "a reasonable

expectation of successfully producing a composition that is non-irritating with optimized bioadhesion, sprayability, viscosity, without compromising the stability of the emulsion," this is not the issue at hand. The issue is not whether this composition may be produced, but how it may be produced.

The Examiner did not provide any support in Sonne that a removal of a crucial ingredient (the solvent for the active agent) of Sonne would, in fact, optimize the composition or even provide composition having identical or similar chemical and/or pharmacokinetic properties. Without this support, the Examiner engages in speculation and hindsight reasoning for the expectation of successfully producing the optimized composition through the removal of the solvent from the composition.

As discussed above, Sonne clearly distinguishes solvents and emulsifiers thus teaching that the compounds providing for these two functionalities are not interchangeable. The proper analysis of Sonne further supports a position that Sonne teaches that Vitamin E is a suitable emulsifier, rather than a suitable solvent. Therefore, one of skill in the art would not be motivated to exclude a solvent α-tocopherol from the compositions of Sonne, and to replace it with an emulsifier, in order to arrive at the compositions of the instant invention. In other words, it is unlikely that one of skill in the art would have reasonably guessed that the solution

of a water-insoluble compound in a hydrophobic solvent would be "optimized" by removing the solvent. Accordingly, Appellants respectfully submit that Sonne does not provide a reasonable expectation of producing a stable emulsion of a water-insoluble drug without the compounds described as useful tocopherol-based solvents.

d. Replacement of tocopherol with Vitamin E TPGS in the composition of Sonne is not routine experimentation because Sonne never disclosed the basic conditions of the instant claims.

As discussed above, Sonne does not suggest removal of an α-tocopherol based solvent from his compositions. The Examiner attempts to overcome this deficiency by arguing that the instant composition could be produced by routine experimentation with concentrations of different compounds in Sonne's composition. Appellants respectfully disagree and submit that experimentation is routine when it is performed within a general framework of prior art. See, e.g., *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) ("where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation"). Otherwise, just about every experimental procedure may be considered routine: every lab technician or an apprentice in the relevant field is expected to know, for example,

how to mix ingredients, do enzymatic digestions, or combine known electrical elements by soldering.

An example of routine experimentation most relevant to this case is finding optimal values relatively close to the borders of the prior art range. In this scenario, the experimentation may be considered routine if the ranges are close enough that one skilled in the art would have expected that the claimed and the prior art compositions have the same properties. *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), *emphasis added*.

In this case, the general conditions of the claim are not disclosed by Sonne. As noted above, all compositions disclosed in Sonne include an α-tocopherol based solvent, and Vitamin E TPGS is not among these disclosed or suggested solvents. Sonne all but explicitly excluded Vitamin E TPGS from the list of α-tocopherol derivatives suitable as solvents.

Sonne did not disclose or suggest the compositions comprising at least 70% aqueous phase wherein the amount of α-tocopherol-based solvent, which does not include the ethoxylated derivative of vitamin E such as Vitamin E TPGS, is so

close to zero that one of skill in the art would have expected that the disclosed compositions and the instantly claimed compositions have the same properties.

It follows from the disclosure of Sonne that the proposed tocopherol-based solvents and Vitamin E TPGS have different properties and therefore are not functionally interchangeable, as discussed above. Further, Sonne teaches that tocopherol-based solvent is an "oily phase" containing the active agent. Sonne Col 4, ln 4. The choice of words "oily phase" assumes hydrophobic water-insoluble properties. On the other hand, Sonne describes Vitamin E TPGS as a water-soluble ampiphilic substance which is soluble in water. Sonne, Col. 4, lns 33-34 and 37-38.

In the broadest reasonable interpretation of Sonne, relevant to the amount of the solvent, the solvent should be present in a sufficient amount to dissolve the active agent. See, e.g., Col 15, lns 42-46 (disclosing a composition comprising "an amount of … at least one tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof <u>sufficient to dissolve the active agent in the tocopherol-based phase</u>"). Emphasis added. Thus, the solvent <u>must</u> be present in a functionally meaningful amount. If the solvent is absent, then, by definition, its amount is insufficient to dissolve the active agent. Thus, one of ordinary skill in the art would not consider that the composition wherein the active agent is

dissolved in an α-tocopherol-based solvent (which, according to Sonne, excludes Vitamin E TPGS, as argued above) has identical or similar properties to a composition wherein the active agent is NOT dissolved in these solvents.

In each example of Sonne that disclosed both Vitamin E TPGS and α-tocopherol, the amount of the former was less than the amount of the latter. In fact, the smallest ratio of α-tocopherol to Vitamin E TPGS was 2 (see Example 17, Col. 12, lns 27-34) meaning that the amount of a solvent (i.e., α-tocopherol) was twice the amount of Vitamin E TPGS. Thus, the amount of Sonne's tocopherol based solvents is not relatively cloze to zero. Suggesting otherwise and considering that the amount of Vitamin E TPGS is less than the amount of tocopherol-based solvent, leads to a conclusion that, if anything, Sonne disclosed the composition without Vitamin E TPGS, thus making Sonne even less relevant to the instant claims.

Accordingly, one of skill in the art would not have realized that the composition without Sonne's α-tocopherol-based solvent and the composition with Sonne's α-tocopherol-based solvent would have the same properties.

Therefore, Appellants respectfully submit that experimentation leading to compositions which have no tocopherol or other tocopherol-based solvents, except Vitamin E TPGS, is beyond routine.

Therefore, for at least these reasons, claims 1, 6, 10, 16, and 22-25 are not obvious in view of Sonne.

2. Claims 13, 14, 15, 26, and 27.

Claim 15 is the independent claim of the group. It is drawn to a composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, consisting of: (a) from about 5 μg/ml to about 5 mg/ml of a corticosteroid in dissolved form; (b) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E, wherein said ethoxylated derivative of vitamin E is the sole vitamin E component of the composition; (c) at least about 70 weight percent aqueous phase; and (d) from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable cosolvent comprising propylene glycol, polyethylene

glycol having a molecular weight between about 200 and 4000, glycerol, ethoxydiglycol, glycofurol, and ethanol, or a combination thereof.

a) Similarly to the independent claims 1 and 16, the independent claim 15 excludes tocopherol-based solvents, and therefore, is not obvious over Sonne for the same reasons.

Similarly to independent claims 1 and 16, claim 15 requires that the "ethoxylated derivative of vitamin E is the sole vitamin E component of the composition." Therefore, the reasons of non-obviousness of claims 1 and 16 are applicable to non-obviousness of claim 15. Specifically, Appellants respectfully re-iterate that removal of Sonne's tocopherol-based solvent and retention of its desired function is evidence of non-obviousness, that Sonne defines Vitamin E-TPGS as an emulsifier, not as a tocopherol derivative solvent thus clearly distinguishing those functionalities, that there is no reasonable expectation of success from Sonne that use of the vitamin E-TPGS emulsifier as a sole vitamin E compound is sufficient to administer insoluble drugs in a stable emulsion, and that removal of Sonne's tocopherol-based solvent is not routine experimentation because Sonne did not disclose the basic conditions of the instant claims.

b) Sonne does not disclose or suggest replacement of the tocopherol-based solvent with a co-solvent.

Sonne discloses the use of co-solvents, such as "[v]egetable oils such as sesame- or olive- or fractionated coconut oil, alcohols such as ethanol, propylene glycol, glycerol, polyethylene glycol or benzyl alcohol; or triacetin." Sonne, Col 6, lns 51-53. Thus, the additional issue which needs to be analyzed is whether Sonne suggested replacement of a tocopherol-based solvent with a co-solvent recited in claim 15.

Appellants respectfully submit that Sonne does not disclose or suggest replacement of a tocopherol-based solvent with one of these co-solvents. This argument has not been presented before to the attention of the Examiner.

The prefix "co-" as in "co-solvents" assumes that these solvents act together with other solvents. For example, *Webster Collegiate Dictionary*, 10th Ed., Merriam-Webster, Inc., on page 218 defines "co-" as, *inter alia*, "with" or "together" or "having a usu. lesser share of responsibility." See Exhibit K. Thus, these solvents must act together with something else.

Sonne discloses co-solvents in several portions of the specification. In one portion, Sonne discloses that

> The compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent. However such solutions are viscous, and the viscosity may be too high for certain applications, for example to achieve a sprayable formulation for nasal application.
>
> Viscosity can be reduced by addition of co-solvents such as ethanol, but this is less desired, since solutions of this kind tend to be irritating to certain mucosal tissues.
>
> Alternatively, the tocopherol solutions may be emulsified, to obtain formulations of lower viscosity.

Col 3, ln 65- Col 4, ln 2, emphasis added. Thus, Sonne teaches adding either emulsifier such as Vitamin E TPGS, or co-solvents. Regardless of which alternative is selected, the composition still must contain α-tocopherol.

In the other portion of Sonne, the reference to co-solvents is tied to the "formulations according to the invention." Sonne, Col. 6, ln 47-50. As noted above, all formulations according to the invention of Sonne contain an α-tocopherol based solvent, and Vitamin E TPGS is not among those solvents.

Appellants further respectfully assert that the replacement of tocopherol-based solvent with one or more of the aforementioned co-solvents should not be considered routine experimentation. The reason for this assertion is that any composition lacking Sonne's tocopherol-based solvent is outside of Sonne's framework. In other words, no composition of Sonne discloses or suggests the basic description of the instantly claimed composition. Finally, as argued above, the instantly claimed compositions lack Sonne's tocopherol-based solvents and yet retain desirable properties conferred by those solvents.

Therefore, for these reasons, claim 15 and claims 13, 14, 26 and 27 dependent therefrom, are not obvious in view of Sonne.

3. Claim 17

Claim 17 is drawn to a composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, consisting of: (a) from about 5 μg/ml to about 5 mg/ml of a corticosteroid in dissolved form; (b) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E, wherein said ethoxylated

derivative of vitamin E is the sole vitamin E component of the composition; (c) at least about 70 weight percent aqueous phase; and (d) from about 0.1 to about 3 percent by weight of an oil.

a) Similarly to the independent claims 1 and 16, the independent claim 17 excludes tocopherol-based solvents, and therefore, is not obvious over Sonne for the same reasons.

Similarly to claims 1 and 16, claim 17 requires that the "ethoxylated derivative of vitamin E is the sole vitamin E component of the composition." Therefore, the reasons of non-obviousness of independent claims 1 and 16 are applicable to non-obviousness of claim 17. Specifically, Appellants respectfully re-iterate that removal of Sonne's tocopherol-based solvent and retention of its desired function is evidence of non-obviousness, that Sonne defines Vitamin E-TPGS as an emulsifier, not as a tocopherol derivative solvent clearly distinguishing those functionalities, that there is no reasonable expectation of success from Sonne that use of the vitamin E-TPGS emulsifier as a sole vitamin E compound is sufficient to administer insoluble drugs in a stable emulsion, and that removal of Sonne's tocopherol-based solvent is not routine experimentation because Sonne did not disclose the basic conditions of the instant claims.

b) Sonne teaches away from replacement of tocopherol-based solvent with vegetable oils.

Appellants further respectfully submit that Sonne does not teach replacement of his tocopherol-based solvent with a vegetable oil. Appellants respectfully refer the Board's attention to Sonne Col 2 lns 1-3 stating that "[t]riglycerides such as vegetable oils are generally non-irritant, but usually these oils are too poor as solvents to be of any use." Thus, according to Sonne, replacement of Sonne's tocopherol-based solvents with vegetable oil would not be successful. In fact, Sonne disparages the use of oils as solvents, thereby directly teaching away from claim 17 and rendering the composition inoperable. See *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004), *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984), MPEP § 2145.X.D. Therefore, for this additional reason, which is presented here for the first time, claim 17 is not obvious in view of Sonne.

C. Rejection of claims 1, 6, 10, 13-17 and 22-27 over claims 1-7 of U.S. Patent 6,241,969 (the '969 patent) under the doctrine of obviousness-type double-patenting.

In the previous responses, Appellants respectfully requested the Examiner to hold this ground of rejection in abeyance. Appellants thank the Examiner for

granting these requests. Accordingly, the argument below is brought to the Examiner's attention for the first time.

In the analysis of the obviousness-type double-patenting rejection, it is impermissible to consider the disclosure of the '969 patent. See *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992), MPEP § 804[R-5].II.B.1. Therefore, the analysis must be limited to what is disclosed in claims 1-7 of the '969 patent.

Further, an obviousness-type double-patenting rejection can be overcome by filing a terminal disclaimer. See, e.g., Office Action at 6. Appellants respectfully refer to the Terminal Disclaimer which was filed on November 29, 2007 (Exhibit G). The prosecution record does not show any evidence that this Terminal Disclaimer has been rejected.

Therefore, for these reasons, Appellants respectfully submit that his rejection ground has been overcome and respectfully request withdrawal of this ground of rejection.

X. CONCLUSION

For the foregoing reasons, it is submitted that the Examiner's rejection of claims 1, 5-10, 13-17 and 22-27 as obvious in view of Sonne was erroneous, and reversal of the rejection is respectfully requested.

It is submitted further that Examiner's rejection of claims 1, 6, 10, 13-17 and 22-27 over claims 1-7 of the '969 patent under the doctrine of obviousness-type double-patenting was erroneous, and reversal of the rejection is respectfully requested.

Appellants request either that the Board render a decision as to the allowability of the claims, or alternatively, that the application be remanded for reconsideration by the Examiner.

Respectfully submitted,

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XI. CLAIMS APPENDIX

1. (Previously presented) A composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, consisting of:

(a) from about 5 μg/ml to about 5 mg/ml of a corticosteroid in dissolved form;

(b) from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component, wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E, wherein said ethoxylated derivative of vitamin E is the sole vitamin E component of the composition; and

(c) at least about 70 weight percent aqueous phase.

2. (Canceled)

3. (Canceled)

4. (Canceled)

5. (Withdrawn) The composition of claim 1 wherein the corticosteroid comprises beclomethasone dipropionate.

6. (Previously presented) The composition of claim 1 wherein the corticosteroid comprises budesonide.

7. (Withdrawn) The composition of claim 1 wherein the corticosteroid comprises triamcinolone acetonide.

8. (Withdrawn) The composition of claim 1 wherein the corticosteroid comprises fluticasone propionate.

9. (Withdrawn) The composition of claim 1 wherein the corticosteroid comprises flunisolide.

10. (Previously presented) The composition of claim 1 wherein the high-HLB surfactant component comprises at least 50% by weight tocopheryl polyethylene glycol 1000 succinate.

11. (Canceled)

12. (Canceled)

13. (Previously presented) The composition of claim 15 wherein the high-HLB surfactant component comprises at least 75% by weight of an ethoxylated derivative of vitamin E.

14. (Previously presented) The composition of claim 15 wherein the high-HLB surfactant component comprises at least 90% by weight of an ethoxylated derivative of vitamin E.

15. (Previously presented) A composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, consisting of:

(a) from about 5 μg/ml to about 5 mg/ml of a corticosteroid in dissolved form;

(b) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E, wherein said ethoxylated derivative of vitamin E is the sole vitamin E component of the composition;

(c) at least about 70 weight percent aqueous phase; and

(d) from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable cosolvent comprising propylene glycol, polyethylene glycol having a molecular weight between about 200 and 4000, glycerol, ethoxydiglycol, glycofurol, and ethanol, or a combination thereof.

16. (Previously presented) A composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, consisting of:

(a) from about 5 μg/ml to about 5 mg/ml of a corticosteroid in dissolved form;

(b) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E, wherein said ethoxylated derivative of vitamin E is the sole vitamin E component of the composition;

(c) at least about 70 weight percent aqueous phase; and

(d) from about 0.1 to about 3 percent by weight of a low HLB surfactant having an HLB below about 8.

17. (Previously presented) A composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, consisting of:

(a) from about 5 μg/ml to about 5 mg/ml of a corticosteroid in dissolved form;

(b) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E, wherein said ethoxylated derivative of vitamin E is the sole vitamin E component of the composition;

(c) at least about 70 weight percent aqueous phase; and

(d) from about 0.1 to about 3 percent by weight of an oil.

18. (Withdrawn) A method for administering a therapeutic dosage of a corticosteroid to the respiratory tract, comprising:

(a) providing a corticosteroid composition comprising:

(1) from about 5 μg/ml to about 5 mg/ml of a corticosteroid in dissolved form;

(2) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E; and

(3) at least about 70 weight percent aqueous phase;

(b) aerosolizing the corticosteroid composition; and

(c) administering a therapeutic effective dosage of the aerosol of the corticosteroid composition by inhalation.

19. (Withdrawn) The method of claim 18 wherein the corticosteroid composition consists essentially of said corticosteroid, said aqueous phase, and said high-HLB surfactant.

20. (Withdrawn) A method for administering a therapeutic dosage of a corticosteroid to the nasal passage, comprising:

(a) providing a corticosteroid composition comprising:

(1) from about 50 ug/ml to about 10 mg/ml of a corticosteroid in dissolved form;

(2) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% of an ethoxylated derivative of vitamin E;

(3) at least about 70 weight percent aqueous phase;

(b) administering a therapeutic effective dosage of the corticosteroid composition by nasal inhalation.

21. (Withdrawn) A method of preparing a diluted corticosteroid composition containing the corticosteroid in dissolved form, comprising:

(a) dissolving a corticosteroid compound into a molten pharmaceutically acceptable high-HLB surfactant component, wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% of an ethoxylated derivative of vitamin E;

(b) subsequently blending the molten high-HLB surfactant component containing the dissolved corticosteroid with an aqueous phase, wherein the aqueous phase is present in an amount of at least about 70 weight percent, and the

high-HLB surfactant component is present in an amount of from about 0.1 to about 20 weight percent of the diluted corticosteroid composition.

22. (Previously presented) The composition of claim 1 wherein the ethoxylated derivative of vitamin E comprises at least 75% by weight of the high-HLB surfactant component.

23. (Previously presented) The composition of claim 1 wherein the ethoxylated derivative of vitamin E comprises at least 90% by weight of the high-HLB surfactant component.

24. (Previously presented) The composition of claim 1 wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

25. (Previously presented) The composition of claim 1 wherein the high-HLB surfactant component comprises at least 90% by weight tocopheryl polyethylene glycol 1000 succinate.

26. (Previously presented) The composition of claim 15 wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

27. (Previously presented) The composition of claim 15 wherein the high-HLB surfactant component comprises at least 90% by weight tocopheryl polyethylene glycol 1000 succinate.

28. (Withdrawn) The method of claim 18 wherein the ethoxylated derivative of vitamin E comprises at least 75% by weight of the high-HLB surfactant component.

29. (Withdrawn) The method of claim 18 wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

30. (Withdrawn) The method of claim 20 wherein the ethoxylated derivative of vitamin E comprises at least 75% by weight of the high-HLB surfactant component.

31. (Withdrawn) The method of claim 20 wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

32. (Withdrawn) The method of claim 21 wherein the ethoxylated derivative of vitamin E comprises at least 75% by weight of the high-HLB surfactant component.

33. (Withdrawn) The method of claim 21 wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

XII. EVIDENCE APPENDIX

Exhibit A: Claims as of December 20, 2001

Exhibit B: Requirement for Restriction/Election of October 10, 2006

Exhibit C: Response to Requirement for Restriction/Election of October 10, 2006.

Exhibit D: Office Action of May 31, 2007

Exhibit E: Claims as of November 29, 2007 in response to the Office Action of May 31, 2007

Exhibit F: Office Action of February 11, 2008.

Exhibit G: U.S. Patent No. 6,193,985

Exhibit H: U.S. Patent No. 6,241,969

Exhibit I: Terminal Disclaimer filed on November 29, 2007

Exhibit J: Office Action of April 15, 2009

Exhibit K: Page 218 of *Webster Collegiate Dictionary*, 10th Ed., Merriam-Webster, Inc., 1993.

Exhibit L: PCT application PCT/US99/14351.

XIII. APPENDIX OF RELATED PROCEEDINGS

Applicants or the Assignee is not aware of any related appeals and/or interferences.